Message

From: eu-toxrisk-sab-request@eurtd.com [eu-toxrisk-sab-request@eurtd.com]
on behalf of Magdalini.SACHANA@oecd.org [Magdalini.SACHANA@oecd.org]
Sent: 7/22/2016 9:03:51 AM
To: Derek.KNIGHT@echa.europa.eu; thomas.steger-hartmann@bayer.com; eu-toxrisk-sab@eurtd.com; barton@arttic.eu
CC: Tarja.VIRTA@echa.europa.eu
Subject: [eu-toxrisk-sab] TK research call

Dear All,

Here are some thoughts for the research call on toxicokinetics (TK).

As I am not an expert in the field my suggestions are based on the strategy document on TK that was developed by the JRC the time that I was there and you can have access to it through this link

http://publications.jrc.ec.europa.eu/repository/bitstream/JRC96418/eurl%20ecvam%20toxicokinetics%20strategy.pdf

Based on the gaps and needs identified in this document, you might consider to focus the research in 3 areas:

1) Kinetic modelling

To facilitate the use of PBTK modelling in the risk assessment, there is a need to make in silico ADME prediction tools as well as PBTK modelling tools readily accessible and easy to apply, and to establish good practice in kinetic modelling based on WHO/IPCS, 2010. Consequently, research effort should be directed towards the development of:

- Comprehensive web-based kinetic modelling portals; and
- Good kinetic modelling practice e.g. guidance document.

2) Data collection - Generation and storage of ADME and TK data

Research should also focus on generation and collection of ADME and TK data in readily accessible databases. Sharing of proprietary data could enable the generation of a large, high quality database of 'paired' in vitro and in vivo human data on the same substance that could be used to investigate the predictive value of in vitro data.
This kind of databases are important for ready to use PBTK modelling and essential for developing comprehensive web-based PBTK modelling platforms.

3) Need for in vitro methods

- to measure the passive permeability of internal membranes, such as the blood-brain barrier and the placental barrier as well as active transport across barriers.
- to estimate the involvement of urinary and biliary excretion pathways are the two most relevant excretion pathways.

For your information in the last EAGMST meeting, JRC proposed the establishment of a working group on toxicokinetics that hopefully will take form soon.

Hope it helps,

Have a lovely summer

Magda

From: eu-toxrisk-sab-request@eurtd.com [mailto:eu-toxrisk-sab-request@eurtd.com] **On Behalf Of** KNIGHT Derek
Sent: 01 July, 2016 2:36 PM
To: Thomas Steger-Hartmann; eu-toxrisk-sab@eurtd.com; Benjamin Barton (barton@arttic.eu)
Cc: VIRTA Tarja [EU]
Subject: [eu-toxrisk-sab] EUTox Risk - SAB follow up to meeting at General Assembly & input for teleconference next week

Dear SAB,

I cannot attend the TC next week, but this is a follow-up to the short SAB meeting today:

Regarding engagement of regulators with EU-ToxRisk:

- I have asked the chair of ECHA's Member State Committee (MSC) to seek volunteers from the MS competent authorities to help with EU-ToxRisk. I have suggested the main work would be to have input into the regulatory relevance of case studies & in particular to give a view on any 'mock submissions'. I will keep you up to date.
- I think that the SAB should send an e-mail to both EFSA & EMA to ask for their support, not just let EU-ToxRisk members contact them without warning them! Do you want me to do this? Or Thomas as chair could do this. Please confirm.

My AOB item was to ask the SAB to devise a text for me to send to Dr Christian Desaintes of DG R&I who has sought input on possible EU-funded research on toxickinetics targeted to support read-across justifications for REACH/CLP. This is the background information with my initial thoughts. I have informed Christian that the SAB will help in the further input has asked for. Clearly any research in this area would be of benefit to EU-ToxRisk as it is complementary. At the SAB TC can you arrange for the text of the 'Scope' section to be completed? Then I will send it to Christian. I have had input from within ECHA on the 'title', 'specific challenge' & 'expected impact', but the SAB is welcome to comment to improve these sections if appropriate.

I think we could (loosely) follow the format used by R&I for research Calls, at least to address the key aspects. A good example is that for PHC-33-2015 that was https://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/697-phc-33-2015.html . This means covering:

Topic (i.e .the name), e.g. 'Toxicokinetic prediction tools to enhance the confidence of reading across the toxicological properties between chemical substances to improve predictive human safety testing'

The following aspects of **Topic description**:

Specific challenge, e.g.

'A barrier to the successful use of read-across in regulatory toxicology, such as for the REACH & CLP Regulations, is establishing that the toxicokinetic (TK) behaviour of the 'source' & 'target' substance(s) are sufficiently similar that the validity of reading across the toxicology results of the tested 'source' substance to the untested 'target' substance is not compromised. TK covers Absorption (including the rate), Distribution, Metabolism & Excretion; hence this is commonly referred to as ADME. The key question to address is whether (minor) differences in chemical structure between the 'source' & 'target' substances in the read-across case will affect the TK behaviour significantly, i.e. to an extent that will invalidate the read-across justification. Although there are *in silico* & *in vitro* methodologies for predicting TK properties (including rate of absorption), these are not necessarily reliable in distinguishing between closely-related structures (as in read-across cases).'

Scope, i.e. take inspiration from the text of the PHC-33-2015 Call, e.g.

'Proposals should capitalise on advances in all relevant fields of science to understand .....with the objectives of developing and validating routine, non-animal approaches for ..... The research may include the development of .....

Proposals should involve, amongst others, research communities, SMEs, industry and regulatory agencies as appropriate. Proposals should demonstrate efficient mechanisms for the co-ordination of activities and exchange of information, and should include a timeline for delivery of test methods.
In line with the Union's strategy for international cooperation[1] in research and innovation, cooperation is encouraged with similar initiatives in the USA and elsewhere, and would be highly beneficial from scientific and economic standpoints'

Somewhere, perhaps in this 'scope' section, you could state that you anticipate a toolkit &/or guidance for use in address the TK issue in read-across justifications (perhaps mention the RAAF & the TK AEs?) covering a wide range of types of chemical substance (in terms of chemical structure, PC properties & toxicological properties) or the scope of the tools/methodologies (in terms of structure etc.).

Also do you have specific suggestions how to go about the research? You suggested using new subacute rat toxicity studies to measure TK. What about other ideas? E.g. collecting existing TK prediction techniques (*in silico & in vitro*) & 'road testing' them in read-across cases (validated against animal TK results) & investigating the suitability of these techniques to distinguish differences resulting from minor differences in chemical structure. Other ideas?

Expected impact, i.e. again adapt the text from the PHC-2015 Call, e.g.:

- Improved toxicological knowledge to encourage 'read across' between chemical substances for use in different research and regulatory domains.
- Advancement of international co-operation in the field of predictive toxicology and human safety testing.
- Reduced use of laboratory animals in safety testing

Dr Derek J Knight
Senior Scientific Advisor
Executive Director's Office
European Chemicals Agency
Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland
Tel. + 358 9 6861 8215
derek.knight@echa.europa.eu
echa.europa.eu

From: eu-toxrisk-sab-request@eurtd.com [mailto:eu-toxrisk-sab-request@eurtd.com] **On Behalf Of** Thomas Steger-Hartmann
Sent: 27 June 2016 09:23
To: eu-toxrisk-sab@eurtd.com
Subject: [eu-toxrisk-sab] EUTox Risk - SAB presentation

Dear colleagues

Thank you all for your valuable feedback. I have tried to incorporate all aspects.

I'll participate Thursday and Friday (arriving late Wednesday evening).

We will certainly include other topics on the fly as they are identified during the GA.

Kind regards

Thomas

Bayer: Science For A Better Life

Bayer Pharma Aktiengesellschaft
BPH-DD-ED-TOX-IT, Investigational Toxicology
Berlin: Building S116-5-523
Wuppertal: Building 514-301
Müllerstraße 178, 13353 Berlin, Germany
Tel: +49 30 468 14256
Fax: +49 30 468 18172
Mobil: +49 170 3326034
E-mail: thomas.steger-hartmann@bayer.com
Web: http://www.bayer.com